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SEED INTELLECTUAL PROPERTY LAW GROUP PLLC
701 FIFTH AVE
SUITE 5400
SEATTLE, WA 98104

EXAMINER	
LEE, JAE W	

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1656	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/542,867	SHINODA ET AL.	
	Examiner	Art Unit	
	JAE W. LEE	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *19 December 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) *2, 3, 9-12, 16, 17, 19-24 and 26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-8,13-15,18,25 and 27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *20 July 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Application status

The previous amendment to claims, filed on 01/09/2006, is acknowledged, wherein Applicants have amended claims 4, 13 and 14, and added claims 23-27.

Claims 1-27 are pending in this application.

Priority

The instant application is the 371 national stage entry of PCT/JP03/00415, filed on 01/20/2003.

Election

Applicant's election of Group I, Claims 1, 4-8, 13-15, 18, 25 and 27, and SEQ ID NOs: 1 and 2 in the response filed on 12/19/2007, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 3, 9-12, 16, 17, 19-24 and 26, and SEQ ID NOs: 3-10 are withdrawn from further consideration by the Examiner, 37 CFR 1.142(b) as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one

or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Objections to the Specification

The specification is objected to for inappropriate notation of an Internet address. On page 12, line 15, Internet address is cited in an unacceptable form. See M.P.E.P. 707.05(e) for the acceptable notation of an Internet address. The examiner suggests the replacement of Internet citations with appropriate references because Internet pages are subjected to frequent changes and deletions and could be different when the public accesses the Internet page to view the exactly same information.

The disclosure is objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Appropriate correction is required.

Claim Objections

Claims 1, 4-8, 13-15, 18, 25 and 27 are objected to because of the following informalities:

Claims 1, 4-8, 13-15, 18, 25 and 27 are objected to for containing non-elected inventions, i.e., SEQ ID NOs: 3-10.

Claim 4 is objected to because it can be improved with respect to form. The Examiner suggests replacing "inserted with" with ---comprising---.

Appropriate correction is required.

Claim Rejections - 35 U.S.C. § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1, 5-8, 13-15, 18, 25 and 27 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claimed product, as written, does not sufficiently distinguish over the naturally occurring product in living organism, i.e., naturally occurring DNA which encodes a juvenile hormone acid methyltransferase in *Bombyx mori* (see pg. 6, 2nd paragraph, and pg. 35-36 of the specification). It is noted by the Examiner that SEQ ID NO: 1 is identical to the naturally occurring polynucleotide sequence of 2890 bp in *Bombyx mori*. Therefore, claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products. In the absence of "the hand of man", naturally occurring products are considered non-statutory subject matter. See Diamond v. Chakrabarty, 447 U.S. 303, 206, USPQ 193 (1980) and M.P.E.P. 2105.

Claims 14, 15 and 27 are rejected under 35 U.S.C. 101 because claims are drawn to non-statutory subject matter. Claims 14, 15 and 27 are drawn to transgenic animals carrying in their genome or at least some of their cells a recombinant genetic

material, which encompass humans. It is PTO policy not to allow claims to humans (1077 O.G. 24 April 1987). The insertion of ---non-human--- before "individual", would overcome this rejection.

Claim Rejections - 35 U.S.C. § 112

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 4-8, 13-15, 18, 25 and 27 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 4-8, 13-15, 18, 25 and 27 dependent therefrom are indefinite in the recitation of "stringent conditions" as the specification does not define what conditions are encompassed by "stringent". While page 11, 2nd paragraph of the specification describes some exemplary conditions which are intended to be stringent, there is nothing to suggest that other conditions would not also be included within the scope of this phrase. In addition, what is considered stringent varies widely depending on the individual situation as well as the person making the determination. Taken together, it is unclear how homologous to the DNA of SEQ ID NO:1 a sequence must be, in order to be included within the scope of these claims.

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 4-8, 13-15, 18, 25 and 27 are rejected under 35 U.S.C. § 112, first paragraph, written description, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The Court of Appeals for the Federal Circuit has recently held that a "written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as be structure, formula [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials." *University of California v. Eli Lilly and Co.*, 1997 U.S. App. LEXIS 18221, at *23, quoting Fiers v. Revel, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) (bracketed material in original). To fully describe a genus of genetic material, which is a chemical compound, applicants must (1) fully describe at least one species of the claimed genus sufficient to represent said genus whereby a skilled artisan, in view of the prior art, could predict the structure of other species encompassed by the claimed genus and (2) identify the common characteristics of the claimed molecules, e.g., structure, physical and/or chemical characteristics, functional characteristics when coupled with a known or disclosed

correlation between function and structure, or a combination of these (paraphrased from *Enzo Biochemical Inc. v. Gen-Probe Inc.* (CAFC (2002) 63 USPQ2d 1609).

According to MPEP 2163.II.A.1, in evaluating a claimed invention for adequate written description, the examiner should determine what the claim as a whole covers. "Claim construction is an essential part of the examination process. Each claim must be separately analyzed and given its broadest reasonable interpretation in light of and consistent with the written description. See, e.g., *In re Morris*, 127 F.3d 1048, 1053-54, 44 USPQ2d 1023, 1027 (Fed. Cir. 1997)."

Claim 1 (claims 4-8, 13-15, 18, 25 and 27 dependent therefrom) is drawn to a genus of DNAs encoding a protein having a juvenile hormone acid methyltransferase activity, according to any one of (a) to (d) below: (a) any DNA encoding a protein comprising *an* amino acid sequence of SEQ ID NO: 2; (b) any DNA comprising *any* coding region for *a* nucleotide sequence of SEQ ID NO: 1; (c) any DNA encoding a protein comprising *an* amino acid sequence of SEQ ID NO: 2, wherein one or more amino acids are substituted, deleted, inserted, and/or added at any location; or (d) any DNA that hybridizes under stringent conditions with *a* DNA comprising a nucleotide sequence of SEQ ID NO: 1. With respect to Claim 1 (a), the recited genus of DNAs encompasses any DNA encoding *an* amino acid sequence of SEQ ID NO: 2, and *any amino acid fragment thereof comprising at least 2 amino acid residues* (italicized for added emphasis). With respect to Claim 1 (b), the recited genus of DNAs encompasses any DNA comprising any coding region, which can be as small as *a single codon* of SEQ ID NO: 1. With respect to Claim 1 (c), the recited genus of DNAs

encompasses any DNA encoding a protein comprising *an* amino acid sequence of SEQ ID NO: 2, *wherein any amino acids are substituted, deleted, inserted, and/or added.* With respect to Claim 1 (d), the recited genus of DNAs encompasses any DNA that hybridizes under stringent conditions with any DNA comprising *a* nucleotide sequence of SEQ ID NO: 1 and *any nucleic acid fragment thereof comprising at least 2 nucleotides.*

Contrary to the recited genera of DNAs encompassing widely variant structures, the disclosure of the specification is limited to an isolated DNA comprising the cDNA sequence from position 125 to 961 of the polynucleotide sequence as set forth in SEQ ID NO: 1, wherein said cDNA encodes a juvenile hormone acid methyltransferase of *Bombyx mori* as set forth in the polypeptide sequence of SEQ ID NO: 2. Other than this single representative species, the specification fails to describe any additional species by identifying any relevant characteristics or properties of the recited genera. For instance, the specification fails to provide any evidence or indication that any fragment of SEQ ID NO: 2, or any number of amino acid substitutions, deletions, insertions, and/or additions within SEQ ID NO: 2, maintains the biological activity or function, i.e., methyltransferase activity. Furthermore, the specification fails to describe how a single codon of SEQ ID NO: 1 can retain a desired biological function such as a juvenile hormone acid methyltransferase activity in the encoded amino acid sequence. Without an adequate written description with respect to how well the aforementioned genera of DNAs are conserved among orthologs, in addition to the characterization of which residues/motifs/domains of the encoded polypeptides are critical for the desired

biological function, one of skill in the art would not have recognized that Applicants were in possession of such widely variant genera of DNAs having a desired juvenile hormone acid methyltransferase activity because the relevant art does not provide such information.

With respect to Claim 18, the recited genus of oligonucleotides encompasses any 15 nucleotides or more, wherein the oligonucleotide is complementary to the DNA of Claim 1 or its complementary strand. Given how the term "complementary" is defined on pg. 26, lines 8-11 of the specification as to mean "not only nucleotide sequences completely complementary to a continuous nucleotide sequence of at least 15 nucleotides, but also those with a homology of at least 70%, preferably at least 80%, more preferably 90%, and most preferably 95% or more at the nucleotide sequence level," and taking into consideration, how broad the genus of DNAs in Claim 1 is, the recited genus of Claim 18 encompasses widely variant structures of oligonucleotides. However, the disclosure of specification is limited to a couple of specific primers, i.e., SEQ ID NOs 25 and 26 consisting of 30 bp. Such limited disclosure of the specification does not adequately provide written description and/or adequate representative species for the recited genus of oligonucleotides, which encompasses oligonucleotides having 16, 17, 18, 19, 20, ...all the way up to, 2887, 2888, 2889 or 2890 bp with a homology of at least 70 % to SEQ ID NO: 1. Please refer to the M.P.E.P. section 2163 [R-5] under II. A. 3. (a). (ii) for more details with respect to sufficient number of representative species that should be disclosed to describe a widely variant genus.

With regard to claims 13-15, 25 and 27, the scope of invention as claimed encompasses any transgenic cells/plants/animals/humans (i.e. any insect, fish, reptile, mammal, etc, in addition to any plant) comprising the DNA of claim 1.

Applicant is referred to the guidelines for Written Description Requirement published January 5, 2001 in the Federal Register, Vol.66, No.4, pp.1099-1110 (see <http://www.uspto.gov>). In analyzing whether the written description requirement is met for the claimed invention, it is first determined whether a claimed genus have been described through sufficient description of a representative number of species by their complete structure and function. Although, it is not realistic to expect the description of "complete structure" of an animal, or even a cell, the phenotype a transgenic animal with desired traits remains unpredictable phenomenon because it is the result of a complex interaction between animal genetics and environment. Therefore, the inquiry required by this portion of the written description guidelines is interpreted to be whether the phenotypic consequences of altering the genotype have been described especially in view of the state of the transgenic art.

In this case, the Applicants' disclosure is not representative of the products claimed. The claims encompass any transgenic insects/plants/animals/humans (i.e. any insect, fish, reptile, mammal, etc, in addition to any plant). Next, it is then determined whether a representative number of species have been sufficiently described. The specification fails to disclose even a single transgenic insect/plant/animal considering the scope of the invention as claimed in view of the state of transgenic art which clearly reflects that making any and all plants and animals is

considered highly unpredictable (infra: see enablement issues). The limited disclosure in the specification is not deemed sufficient to reasonably convey to one skilled in the art that applicants were in possession of invention as putatively claimed herein. Thus, it is concluded that the written description requirement is not satisfied for the scope of invention as claimed.

Taken together, the specification fails to provide adequate written description for the recited genera of DNAs and transgenic organisms to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Applicants are referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

Claims 1, 4-8, 13-15, 18, 25 and 27 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, because the specification, while being enabling for an isolated DNA comprising the cDNA sequence from position 125 to 961 of the polynucleotide sequence as set forth in SEQ ID NO: 1, wherein said cDNA encodes a juvenile hormone acid methyltransferase of *Bombyx mori* as set forth in the polypeptide sequence of SEQ ID NO: 2, does not reasonably provide enablement for a DNA encoding a protein having a juvenile hormone acid methyltransferase activity, according to any one of (a) to (d) below: (a) any DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2; (b) any DNA

comprising any coding region for *a* nucleotide sequence of SEQ ID NO: 1; (c) any DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, wherein one or more amino acids are substituted, deleted, inserted, and/or added at any location; or (d) any DNA that hybridizes under stringent conditions with *a* DNA comprising a nucleotide sequence of SEQ ID NO: 1 as encompassed by the claims. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The factors to be considered in determining whether undue experimentation is required are summarized In re Wands 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988). The Court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation' (Wands, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or

unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(A) The breadth of the claims: According to MPEP 2164.04, "[b]efore any analysis of enablement can occur, it is necessary for the examiner to construe the claims…and explicitly set forth the scope of the claim when writing an Office action." Also, MPEP 2164.08 states, "[a]ll questions of enablement are evaluated against the claimed subject matter. The focus of the examination inquiry is whether everything within the scope of the claim is enabled. Accordingly, the first analytical step requires that the examiner determine exactly what subject matter is encompassed by the claims…claims are to be given their broadest reasonable interpretation that is consistent with the specification."

Claims are drawn to a DNA encoding a protein having a juvenile hormone acid methyltransferase activity, according to any one of (a) to (d) below: (a) any DNA encoding an amino acid sequence of SEQ ID NO: 2 and *any amino acid fragment thereof comprising at least 2 amino acid residues*; (b) any DNA comprising any coding region, which can be as small as a single codon, for a nucleotide sequence of SEQ ID NO: 1; (c) any DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, *wherein any amino acids are substituted, deleted, inserted, and/or added*; or (d) any DNA that hybridizes under stringent conditions with any DNA comprising a nucleotide sequence of SEQ ID NO: 1 and *any fragment thereof comprising at least 2 nucleotides* (italicized for added emphasis). However, the disclosure of the specification is limited to an isolated DNA comprising the cDNA sequence from position 125 to 961 of

the polynucleotide sequence as set forth in SEQ ID NO: 1, wherein said cDNA encodes a juvenile hormone acid methyltransferase of *Bombyx mori* as set forth in the polypeptide sequence of SEQ ID NO: 2.

Claims 13-15, 25 and 27 are drawn to any transformed cell retaining the DNA of Claim 1 or any individual or any insect transformed with the DNA of Claim 1, which can be broadly interpreted to encompass transgenic individuals or organisms, including insects, animals, plants or humans. However, the specification discloses a single example of transforming an *E. coli* host cell with an isolated DNA comprising the cDNA sequence from position 125 to 961 of the polynucleotide sequence as set forth in SEQ ID NO: 1.

Claim 18 is drawn to any oligonucleotide comprising any 15 nucleotides or more, wherein the oligonucleotide is complementary to the DNA of Claim 1 or its complementary strand, wherein the term "complementary" means "not only nucleotide sequences completely complementary to a continuous nucleotide sequence of at least 15 nucleotides, but also those with a homology of at least 70%, preferably at least 80%, more preferably 90%, and most preferably 95% or more at the nucleotide sequence level (see on pg. 26, line 8-11 of the specification). However, the disclosure of the specification is limited to a couple of specific primers that hybridize to SEQ ID NO: 1.

With regard to claims 13-15, 25 and 27, the scope of invention encompasses any transgenic cells/plants/animals/humans (i.e. any insect, fish, reptile, mammal, plant, etc) comprising the DNA of claim 1. However, the specification fails to disclose even a single transgenic plant/animal which comprises the DNA of claim 1. Since the

specification fails to disclose the invention as claimed, it would require an extensive and undue amount of experimentation to practice the invention as claimed, especially in view of the fact that making transgenic plants/animals across the entire plant and animal kingdoms are considered highly unpredictable.

Taken together, the enablement provided by the specification, which is limited to an isolated DNA comprising the cDNA sequence from position 125 to 961 of the polynucleotide sequence as set forth in SEQ ID NO: 1, wherein said cDNA encodes a juvenile hormone acid methyltransferase of *Bombyx mori* as set forth in the polypeptide sequence of SEQ ID NO: 2, and a transformed *E. coli* host cell comprising said DNA is not commensurate with the above-described, broad scope of DNAs, oligonucleotides, transformed cells, and individuals encompassed by the claims.

(B) The amount of direction provided by the inventor and (C) The existence of working examples: The specification discloses an isolated DNA comprising the cDNA sequence from position 125 to 961 of the polynucleotide sequence as set forth in SEQ ID NO: 1, wherein said cDNA encodes a juvenile hormone acid methyltransferase of *Bombyx mori* as set forth in the polypeptide sequence of SEQ ID NO: 2. The specification teaches transforming an *E. coli* host cell comprising said DNA to express the juvenile hormone acid methyltransferase. The specification also teaches the purification of the juvenile hormone acid methyltransferase (SEQ ID NO: 2) and assaying for the enzymatic activity (Example 4, pg. 37). The specification further teaches an asserted utility of the claimed DNA taught in the prior art (pg. 2, 3rd paragraph) as capable of being used to initiate or inhibit metamorphosis. However, the

specification fails to provide how it could be used to regulate reproduction, blastogenesis, behavior, polymorphism, or life span of an arthropod as recited in Claim 5. Also, the specification fails to disclose any specific guidance for alteration of the DNA sequence of SEQ ID NO: 1 with an expectation that polypeptides, and variants or fragments thereof, encoded by said DNA, will maintain the desired activity/utility. Moreover, the specification fails to provide guidance for using those DNAs and encoded polypeptides that do not have juvenile hormone acid methyltransferase activity, e.g., those polypeptides that are non-functional. In the absence of such guidance, a skilled artisan has no expectation that the DNA of SEQ ID NO: 1 can be altered, *e.g.,* by deletion, insertion, substitution, and/or addition, and maintain the biologically desired activity in the encoded polypeptide.

Regarding the transformed cells and individuals of Claims 13-15, 25 and 27, the specification only discloses a single working example of *E. coli* host cell comprising the cDNA sequence from position 125 to 961 of the polynucleotide sequence as set forth in SEQ ID NO: 1. Other than this example, the specification fails to disclose specific guidance for making and using transgenic insect, animal, plant or human cells/organisms. In the absence of such guidance, a skilled artisan has no expectation of achieving the desired effects of using claimed DNA, especially in those cells/organisms that do not normally synthesize or secrete the juvenile hormone, which is exclusively made by a limited species of insects.

(D) The state of the prior art; (E) The level of one of ordinary skill; and (F) The level of predictability in the art: Since the DNA sequence encoding a polypeptide

determines protein's structural and functional properties, predictability of which DNA sequence can be used while obtaining the desired function in the encoded protein requires a knowledge of and guidance with regard to which nucleic acids in the DNA sequence, if any, are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the DNA sequence relates to the protein's structure and its desired function. In addition, the scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of different DNA sequences.

While recombinant and mutagenesis techniques are known, it is not routine in the art to screen for multiple substitutions, deletions, insertions or modifications, as encompassed by the instant claims. Also, the positions within a DNA sequence where nucleic acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility in the encoded protein are limited and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

For example, Branden et al. ("Introduction to Protein Structure", Garland Publishing Inc., New York, 1991) teach "[p]rotein engineers frequently have been surprised by the range of effects caused by single mutations that they hoped would change only one specific and simple property in enzymes" and "[t]he often surprising results of such experiments reveal how little we know about the rules of protein stability… …they also serve to emphasize how difficult it is to design *de novo* stable

proteins with specific functions" (page 247). Therefore, a skilled artisan would recognize the high level of unpredictability in altering a DNA encoding a juvenile hormone acid methyltransferase with an expectation that it would maintain the desired methyltransferase activity.

With regard to Claims 13-15, 25 and 27, the state of transgenic art at the time of filing was such that phenotype of an animal is determined by a complex interaction of genetics and environment. The phenotype examined in a transgenic and knock out model is influenced by genetic background, which is the collection of all genes present in an organism that influence a trait or traits. The genes may be part of same biochemical or signaling pathway or of an opposing pathway or may appear unrelated to the gene being studied. Furthermore, allelic variations and the interactions between the allelic variants also influence a particular phenotype. These effects can dramatically alter the observed phenotype and therefore can influence the transgenic or knockout models.

Furthermore, the transgene expression and physiological consequences of transgene products in non-mouse mammals are not always accurately predicted among various species of mammals. The lack of understanding of essential genetic control elements make it difficult to predict the behavior of any transgene in any animal because the transgene expression is influenced by position effect in transgenic animals. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, are the important factors that govern the expression of a transgene. The cis acting elements of one species may

interact with different trans-activating factors in other species. For example, the introduction of human growth hormone transgene in mice results in mammoth mouse phenotype, where as expression of the same transgene in pig results in premature death of transgenic pigs. Furthermore, many biochemical pathways are plastic in nature, which reflects the ability of the embryo to use alternative gene when the preferred gene is modified. It is known in the art that the level and the specificity of a transgene as well as the phenotype of the transgenic animal are greatly dependent upon the specific expression vector used. The individual gene of interest, promoter, enhancer, coding or non-coding sequences present in the transgene construct and the site of integration, for example are the important factors that govern the expression of a transgene.

In addition, multicellular organisms are the current evolutionary summation of more than one billion years of selection. Their complexity means that even a humble mouse cannot be used as a simple tool. For example, extensive phenotype tests even in mice have shown that abnormal phenotypes were sometimes detected in physiological areas where they were not initially anticipated, or only manifested under certain conditions, emphasizing the need for careful phenotypic investigation. Nevertheless, the effect of some genes became evident only upon inactivation of another gene, pointing to the phenomenon of biological robustness. Therefore, considering the scope of invention as claimed, at issue, under the enablement requirement of 35 U.S.C. 1 12, first paragraph is whether, given the Wands-factors, the experimentation was undue or unreasonable under the circumstances.

"Experimentation must not require ingenuity beyond that to be expected of one of ordinary skill in the art." See Fields v. Conover, 443 F.2d 1386, 170 USPQ 276 (CCPA 1970). The state of the transgenic art clearly concludes that poor embryo survival, low transgene integration rate and unpredictable transgene behavior are the three primary contributors that determine the fate of a transgenic animal made. see Taft et al. (Trends in Genetics 22(12):649-653, 2006); Linder (Lab. Anim. 30(5):34-39, 2001); Bilbo et al. (Lab. Anim. 30(1):24-29, 2001); Holschneider et al. (Int. J. Dev. Neuroscience 18 :615-618, 2000); Wood (Comp. Med. 50(1): 12-15, 2000); Sigmund (Arterioscler. Throm. Vasc. Biol. 20:1425-1429, 2000); Kappel et al. (Current Opinion in Biotechnology 3:558-553, 1992).

In instant case, making any transgenic cells/plants/animals/humans (i.e. any insect, fish, reptile, mammal, plant, etc) comprising the DNA of claim 1 is not considered routine in the art, and without sufficient guidance for a method of making a particular species, the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. It is noted that the unpredictability of a particular area may alone provide reasonable doubt as to the accuracy of the broad statement made in support of enablement of claims. See Ex parte Singh, 17 USPQ2d 1714 (BPAI 1991). Therefore, one skill in the art would have to engage in excessive and undue amount of experimentation to exercise the invention as claimed.

(G) The quantity of experimentation needed to make or use the invention based on the content of the disclosure: While methods of isolating or generating variants of a polypeptide were known in the art at the time of the invention, it was not routine in the

art to screen by a trial and error process for all DNA sequences that encode juvenile hormone acid methyltransferase polypeptides and fragments thereof comprising at least 2 amino acid residues, optionally having a substantial number of substitutions, deletions, insertions or modifications, as encompassed by the claims and screen and isolate those proteins having the desired activity/utility, i.e., juvenile hormone acid methyltransferase activity, particularly without expectation that these variants will maintain the desired enzymatic activity.

Regarding the transformed cells and individuals of Claims 13-15, 25 and 27, it was not routine in the art to make and use any transgenic cell/organism comprising claimed DNA to achieve some desirable effects without knowledge of whether the encoded protein has the ability to achieve such an effect and without the necessary guidance for making such a transgenic cell/organism, especially those that do not normally synthesize or secrete juvenile hormone.

In view of the broad scope of the claims, the lack of guidance and working examples provided in the specification, and the high degree of unpredictability as evidenced by the prior art, undue experimentation would be necessary for a skilled artisan to make and use the entire scope of the claimed invention. Applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of claimed inventions having the desired biological characteristics is

unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claim Rejections - 35 U.S.C. § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. § 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 5, 13, 14, 18, 25 and 27 are rejected under 35 U.S.C. § 102(b) as being anticipated by Gunawardene et al. (The shrimp FAMeT cDNA is encoded for a putative enzyme involved in the methylfarnesoate (MF) biosynthetic pathway and is temporally expressed in the eyestalk of different sexes, Insect Biochemistry and Molecular Biology Volume 31, Issue 11, October 2001, Pages 1115-1124, see IDS) in view of the evidentiary reference pBluescript® II XR cDNA Library Construction Kit Manual.

The instant claims are drawn to a DNA encoding a protein having a juvenile hormone acid methyltransferase activity, according to any one of (a) to (d) below: (a) a DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2; (b) a DNA comprising a coding region for a nucleotide sequence of SEQ ID NO: 1; (c) a DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, wherein one or more amino acids are substituted, deleted, inserted, and/or added; or (d) a DNA that

hybridizes under stringent conditions with a DNA comprising a nucleotide sequence of SEQ ID NO: 1.

It is noted by the Examiner that "methyl farnesoate [MF] in crustaceans is a hormone homologous to juvenile hormone" (see paragraphs [0074] and [0081] of the specification). Further, the reference of Gunawardene et al. teaches that "Methylfarnesoate (MF) is the unepoxidized analogue of the juvenile hormone III (JH III)" (see first paragraph of the Introduction). Therefore, MF is interpreted to be a type of juvenile hormone.

The reference of Gunawardene et al. teaches the cDNA library construction of the shrimp *Metapenaeus ensis,* and subsequent cloning, characterization and expression of FAMeT gene of the shrimp *Metapenaeus ensis.* Said reference specifically teaches a cDNA sequence encoding a juvenile hormone acid methyltransferase, i.e., farnesoic acid methyltransferase (FAMeT) of the shrimp *Metapenaeus ensis*, which catalyses the methylation of the MF (juvenile hormone) acid to produce MF in a similar manner to that of the insects (see 2nd paragraph of the Introduction), which anticipates claim 1 in the recitation of "[a] DNA encoding a protein having a juvenile hormone acid methyltransferase activity, according to any one of (a) to (d) below: (a) a DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, 4, 6, 8, or 10; (b) a DNA comprising a coding region for a nucleotide sequence of SEQ ID NO: 1, 3, 5, 7, or 9; (c) a DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, 4, 6, 8, or 10, wherein one or more amino acids are substituted, deleted, inserted, and/or added; or (d) a DNA that hybridizes under

stringent conditions with a DNA comprising a nucleotide sequence of SEQ ID NO: 1, 3, 5, 7, or 9." Although there was no significant similarity in the sequence alignment result of the shrimp FAMeT (Genbank Accession Number AF333042) taught in said reference and Applicants' SEQ ID NO: 1, said reference anticipates the claimed DNAs because said DNAs encompass a DNA comprising any coding region, which can be as small as a single codon of SEQ ID NO: 1, and a DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, wherein any amino acids are substituted, deleted, inserted, and/or added. Said reference also teaches a vector, i.e., pBluescript cloning vector, comprising said cDNA (see Materials and methods under Preparation of total RNA and RT-PCR), which anticipates claims 4 and 5. It is noted by the Examiner that crustaceans belong to the genus of arthropods, and are different from insects. It is also noted by the Examiner that the recitation of "for regulating molting/metamorphosis, reproduction, diapause, blastogenesis, behavior, polymorphism, or life span of an arthropod..." is an intended use, which is accorded limited patentable weight because it merely recites the use of a product. Please refer to M.P.E.P. 707.07(f) [R-3], ¶ 7.37.10.

Claim 18 is included in this rejection because the cDNA taught by the reference reads on an oligonucleotide of at least 15 nucleotides which is complementary to the DNA encoding a protein comprising an amino acid sequence of SEQ ID NO: 2, *wherein one or more amino acids are substituted, deleted, inserted, and/or added* (italicized for added emphasis). It is noted by the Examiner that the phrase, "complementary to the DNA of claim 1" in claim 18, is interpreted as "not only nucleotide sequences completely complementary to a continuous nucleotide sequence of at least 15 nucleotides, but also

those with a homology of at least 70%, preferably at least 80%, more preferably 90%, and most preferably 95% or more at the nucleotide sequence level [to the DNA of claim 1]," according to pg. 26, line 8-11 of the specification.

Claims 13, 14, 25 and 27 are included in this rejection because the construction of cDNA library of *M. ensis*, and the cloning of FAMeT using pBluescript vector as taught by Gunawardene et al. utilize transformed *E. coli*, i.e., XL-10 Gold, comprising said cDNA, as evidenced by the reference of pBluescript II XR cDNA Library Construction Kit Manual. Said manual teaches a general methodology for making a cDNA library using transformed *E. coli* with pBluescript vectors on pg. 23. It is noted by the Examiner that the specification does not provide any specific definition for the term "individual." The specification merely states some preferences of what an individual can be, i.e., a genetically transformed arthropod individuals in paragraph [0147]. As such, "[an] individual" which normally would be interpreted as a human individual, is broadly interpreted as encompassing an individual transformant. Therefore, transformed *E. coli* cells are encompassed by the term "[a]n individual" as recited in Claims 14 and 27, and Claims 13, 14, 25 and 27 are anticipated by the teachings of Gunawardene et al. in view of the evidentiary reference of pBluescript manual.

Thus, Gunawardene et al. anticipates the Applicants' claimed invention.

Conclusion

Claims 1, 4-8, 13-15, 18, 25 and 27 are rejected for the reasons as stated above. Applicants must respond to the objections/rejections in this Office action to be fully responsive in prosecution.

The instant Office action is non-final.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jae W. Lee whose telephone number is 571-272-9949. The examiner can normally be reached on 8:00-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Kathleen Kerr Bragdon can be reached on 571-272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/JAE W LEE, PhD/
Examiner, Art Unit 1656

/Kathleen Kerr Bragdon/
Supervisory Patent Examiner, Art Unit 1656